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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/764,057	01/23/2004	Chin-Ming Chang	17273 CON1 CIP1 (AP)	7601

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EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	PAPER NUMBER
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/764,057	CHANG ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02/02/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) *38-45,52 and 53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37,46-51 and 54* is/are rejected.

7)☐ Claim(s) _ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Acknowledgement is made of applicant's filing of amendment/remarks February 02, 2007. By the amendment, claims 1, 15, 13, 26 and 46 have been amended.

2. Applicant's arguments, filed 02/02/07, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1, 13, 33-35, 46-50 and 54 rejected under 35 U.S.C. 102(b) as being anticipated by Lipari (US 4383992).

Lipari discloses a topical ophthalmic solution comprising 0.12% prednisolone such as prednisolone acetate, about 20% beta-cyclodextrin, about 0.5% hydroxypropylmethylcellulose that is useful for the treatment ocular inflammation (Example 1).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 2-12, 14-32, 36-37 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipari (US 4383992) in view of Loftsson (US 5472954), and further in view of Shinohara (5998488).

The teaching of Lipari has been discussed in above 35 USC 102(b) rejection.

Loftsson teaches a method of improving solubility and stability of pharmaceutical actives including prednisolone or prednisone by delivering the pharmaceutical actives in an aqueous solution comprising cyclodextrin (i.e., hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-

cyclodextrin), water-soluble polymer (i.e., hydroxypropyl methylcellulose) and a lipophilic and/or water labile active ingredient (i.e., prednisolone and prednisone) and additives (i.e., buffers, preservatives, pH adjusting agents, chelating agent, etc...), wherein said solution is prepared in various dosage forms including ophthalmic formulation, preferably a sterile, isotonic, buffered aqueous solution (abstract; column 4, line thru column 5, line 50; column 6, line 29 thru column 7, line 43; column 9, line 38-39; column 13, line 65 thru column 14, line 25; column 19, lines 16-31; Example 11).

Shinohara is being supplied as reference to demonstrate the routine knowledge in using secondary agents such as chelating agent EDTA, cyclodextrins (e.g., β-cyclodextrin or γ-cyclodextrin) and NaCl in eye drops or ophthalmic solution.

The teaching of Lipari differs from the claimed invention in the use of cyclodextrin derivatives such as hydroxypropyl-β-cyclodextrin and hydroxypropyl-γ-cyclodextrin and excipients such as preservative, tonicifying agent, buffers and chelating agent. To incorporate such teaching into the teaching of Lipari, would have been obvious in view of Loftsson who teaches the use of cyclodextrin (i.e., hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin) and water-soluble polymer (i.e., hydroxypropyl methylcellulose) in improving solubility and stability of steroid drug such as prednisolone and Shinohara who teaches the routine knowledge in using secondary agents such as EDTA and tonicifying agent such as NaCl in eye drops or ophthalmic solution.

It would have been obvious to one having ordinary skill in the art at the time of the invention was made to prepare the above taught composition in the effective amounts taught by applicant for with a reasonable expectation of success having above-cited references in

combination. Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

With respect to the specific pH range of the claimed composition, generally differences in an concentration or pH range will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such pH range are critical. Where the general conditions of a claim are disclosed in the prior art (especially ophthalmic preparation art), it is not inventive to discover the optimum or workable pH range by routine experimentation.

Response to Arguments

5. Applicant's argument in the response takes the position that Lipari does not teach a cyclodextrin derivative such as cyclodextrin that has been chemically modified.

This argument is not found persuasive. There is no indication in the claims that the required cyclodextrin derivative in the claims 1, 13, 33-35, 46-50 and 54 must be essentially "cyclodextrin that has been chemically modified". Contrary to the applicant's argument, the claims require only "a water soluble cyclodextrin derivative" in which the referenced beta-cyclodextrin already possesses of. Thus, Lipari clearly anticipates the claimed invention in claims 1, 13, 33-35, 46-50 and 54.

Applicant's argument in the response takes the position that the prior art suggests that the claimed combination is not desirable. Applicant alleges that the Loftsson's article (Advanced Drug Delivery Reviews 36 (1999) 59-79) teaches away from the combination of prednisolone

acetate and a cyclodextrin derivative by teaching that carboxylic acid prodrugs are unstable in the presence of cyclodextrins and cyclodextrin derivatives, and that cyclodextrins and cyclodextrin derivatives may decrease the bioavailability of steroids in ophthalmic formulations.

This argument is not found persuasive. Although the Loftsson's article acknowledges that the CD complexation of water soluble drugs may decrease their ophthalmic bioavailability, the Loftsson teaches that CDS are still useful additives in ophthalmic formulations (see Conclusions). In addition, the Loftsson teaches how to overcome such problem (i.e., decrease in bioavailability of the drug) by increasing the viscosity of the aqueous eye drop formulation, for example by incorporating water-soluble polymers such as hydroxypropylmethylcellulose to the CDs (see page 72, left column, para. 3 and conclusion). As similarly recognized by the USP'954, the whole context of the Loftssson's article teaches the usefulness of combining cyclodextrin (i.e., hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin) with water-soluble polymer (i.e., hydroxypropyl methylcellulose) in improving the bioavailability of the lipophilic and/or water labile active ingredient (i.e., prednisolone and prednisone).

As discussed above, the problem of using CDs alone was recognized by the prior art, the modification by adding water-soluble polymer such as hydroxypropylmethylcellulose is taught by the Loftsson (USP'954 as well as the Loftsson's article). Thus, the skilled artisan would have been arrived at the claimed invention in view of the cited references (Lipari (US 4383992) in view of Loftsson (US 5472954), and further in view of Shinohara (5998488) in combination.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching,

suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. No Claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Brian Kwon
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